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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/024,607	11/08/2001	Richard T. Lee	B0801.70231US00	6830

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EXAMINER	
HISSONG, BRUCE D	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 03/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/024,607	LEE, RICHARD T.	
	Examiner	Art Unit	
	Bruce D. Hissong, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-8,10 and 37-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6-8,10 and 37-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/6/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Applicant's Amendment

Formal Matters

1. Applicant's amendments to the claims and specification, and arguments/remarks, received 12/27/2005, are acknowledged and have been made of record.

2. Applicant's have amended claims 1, 6-8, and 10, and have cancelled claims 2, 13, 15-22, 26-29, and 34, and have added new claims 37-48. Therefore, claims 1, 6-8, 10, and 37-48 are currently pending and are the subject of this Office Action.

3. The text of those sections of Title 35, U.S.C. not included in this action can be found cited in full, in the previous office action mailed on 10/07/2005.

Information Disclosure Statement

The information disclosure statement received on 3/6/2006 has been fully considered by the Examiner.

Claim Objections

1. The objection to claim 1, as set forth in the Office Action mailed on 10/07/2005 is withdrawn in response to Applicant's amendment.

2. The objection to claim 2, as set forth in the Office Action mailed on 10/07/2005, is withdrawn in response to Applicant's cancellation of the claim.

3. Claim 8, as well as dependent claims 10 and 42-48, are objected to because the term "the polypeptide" in parts (iii) and (iv) should refer to either the polypeptide of (ii), or should state "said polypeptide". The situation is similar for the term "peptide" in part (iv).

Claim Rejections - 35 USC § 112, first paragraph – enablement

Rejections withdrawn:

1. Rejection of claims 1, 6-8, and 10 under 35 USC § 112, first paragraph, regarding lack of enablement for determining expression of "a fragment of an expression product thereof", as set forth on page 3 of the prior Office Action mailed on 10/07/2005, is withdrawn in response to Applicant's arguments that Fit-1/ST2 fragments can be detected by assays that are well-known in the art. Rejection of claim 2 is rendered moot by Applicant's cancellation of the claim.

2. Rejection of claims 1, 6-8, and 10 under 35 USC § 112, first paragraph, regarding lack of enablement for diagnosis of cardiovascular disease using Fit-1 nucleic acids, polypeptides, or peptides other than those of SEQ ID NO: 1-4, as set forth on pages 4-5 of the prior Office Action mailed on 10/07/2005, is withdrawn in response to Applicant's arguments describing numerous Fit-1 nucleic acid and polypeptide sequences which were known in the art at the time the invention was made. Rejection of claim 2 is rendered moot by Applicant's cancellation of the claim.

Rejections maintained:

3. Claims 8 and 10 remain rejected, and new, dependent claims 42-48 are also rejected under 35 USC § 112, first paragraph, regarding lack of enablement for diagnosis of cardiovascular conditions by monitoring "an antibody which selectively binds the polypeptide or peptide", and "a polypeptide or peptide which binds the antibody of (iv)", as set forth on page 3 of the prior Office Action mailed on 10/07/2005. The Applicant argues, on page 9 of the response received on 12/27/2005, that Fit-1 polypeptides were known in the art prior to the filing of the instant application, and thus a person of ordinary skill in the art would know how to use these polypeptides to conduct standard immunoassays to determine the presence, absence, or level of anti-Fit-1/ST2 antibodies. These arguments have been fully considered and are not deemed persuasive. The Examiner agrees that a person of ordinary skill in the art would posses the technical skill to detect anti-Fit-1/ST2 antibodies. However, the claims read on detecting a Fit-1 antibody from a patient sample. As stated on page 3 of the prior Office Action mailed on

10/07/2005, the specification does not provide any examples of naturally occurring Fit-1 antibodies, or antibodies against Fit-1 polypeptides, that are present in a patient with a cardiovascular disorder. The specification does not teach that anti-Fit-1/ST2 antibodies are present in either normal, healthy settings, or pathological conditions such as cardiovascular disease. It has long been known in the art that the immune system exhibits immunological tolerance to self-proteins such as Fit-1. While antibodies to some self proteins are known in autoimmune disorders, the specification and the prior art does not teach that anti-Fit-1 antibodies are produced in any cardiovascular disease. Therefore, because the claims read on a method of detecting antibodies that would not be predicted to be present in either normal or cardiovascular conditions, a person of ordinary skill in the art would not know how to use such antibodies in a method of diagnosing cardiovascular disease.

4. Claims 1, 6-8, and 10 are rejected, and new, dependent claims 37-48 are also rejected under 35 USC § 112, first paragraph, regarding lack of enablement for methods of assessing "aberrant" expression of Fit-1 nucleic acids, polypeptides, peptides, or antibodies, as set forth on page 4 of the prior Office Action mailed on 10/07/2005. Rejection of claim 2 is rendered moot by Applicant's cancellation of the claim. As stated on page 4 of the prior Office action mailed on 10/07/2005, the specification is enabling for diagnosis of cardiovascular disease by increased Fit-1 expression, but not deceased Fit-1 expression. The Applicant's, on pages 10-11 of the response received on 12/27/2005, point to the description in the specification of increased Fit-1 expression after a cardiovascular event, wherein the elevated Fit-1 expression decreases to baseline levels over a period of time. Based on this disclosure, the Applicant's argue that "aberrant" expression is a more accurate description of the invention than "increased" expression, because each of the observed levels of Fit-1 expression is "aberrant" as compared to the baseline expression, and because as a relative measure, the second observed level is decreased, not increased, relative to the first observed level. These arguments have been fully considered but have not been found persuasive. The term "aberrant", given the broadest reasonable interpretation, can encompass increased or decreased expression. Thus, the term does not define the diagnostic limits of Fit-1 expression levels, whether relative or absolute. Additionally, the claims do not specify the time-line for Fit-1 determination, or the number of times Fit-1 expression should be determined. A person of ordinary skill in the art would not be able to diagnose cardiovascular disease without taking multiple Fit-1 expression measurements

over a period of time. Therefore, because the term "aberrant" can encompass both relative and absolute decreases in Fit-1 levels, the specification is not enabling for diagnosis of cardiovascular conditions by "aberrant" expression of Fit-1. The Examiner suggests the term "aberrant" be further defined in the claim by reciting, as an example, "aberrant expression characterized by an initial increase in Fit-1/ST2 expression.....".

Similarly, claim 8, as well as dependent claims 10 and 42-48, reads on determining the stage of cardiovascular disease by determination of Fit-1 levels. As stated on page 4 of the Office Action mailed on 10/07/2005, the specification does not provide guidance or working examples that would teach a person of ordinary skill in the art to determine a particular stage of any cardiovascular disease. As such, a person of ordinary skill in the art would not be able to correlate Fit-1 expression with any specific stage of a cardiovascular disease, and therefore the specification is not enabling for determining the stage of a cardiovascular disease by assessing Fit-1 levels. The Applicant's response of 12/27/2005 did not address this issue, and therefore the rejection is maintained.

5. Claims 1, 6-8, and 10 remain rejected, and new, dependent claims 37-48 are also rejected under 35 USC § 112, first paragraph, regarding lack of enablement for diagnosis of cardiovascular disease by detecting Fit-1 in a biological sample, as set forth on pages 5-6 of the prior Office Action mailed on 10/07/2005. Rejection of claim 2 is rendered moot by Applicant's cancellation of the claim. In response to the Applicant's arguments on page 14 of the specification, the Examiner acknowledges that the specification is enabling for detecting Fit-1 expression in serum and blood, and also agrees with the Applicant's assertion that Fit-1 nucleic acids, polypeptides, or peptides can be detected in these and other tissues by methods that are known in the art. However, the specification does not teach that expression of Fit-1 in tissues other than blood, serum, or cardiovascular tissue is indicative of any cardiovascular disease. The claims read on determination of Fit-1 in a biological sample, and thus read on potentially any tissue. There is no guidance in the specification that teaches, for example, aberrant Fit-1 expression in skeletal muscle tissue as diagnostic for cardiovascular disease, nor would a skilled artisan be expected to predict that an increase in Fit-1/ST2 in skeletal muscle tissoue would be indicative of a cardiovascular condition. By following the teachings of the specification, a person of ordinary skill in the art would not be able to diagnose cardiovascular disease by determination of Fit-1 in any tissue other than blood, serum, or cardiovascular tissue.

Therefore, the specification is not enabling for diagnosis of cardiovascular disease in all possible biological tissues.

6. Claim 10 remains rejected, and new claims 39 and 45-46 are also rejected under 35 USC § 112, first paragraph, regarding lack of enablement for contacting a sample with a detectable agent, such as "(a) an isolated nucleic acid molecule which hybridizes to the nucleic acid molecule of (i)", as set forth on page 5 of the prior Office Action mailed on 10/07/2005. The Applicants argue on p. 13 of the response received on 12/27/2005, that a person of ordinary skill in the art would have known, at the time the invention was made, of several Fit-1 nucleic acid sequences, and that the skilled artisan would also have the knowledge of expertise to design primers or probes that selectively hybridize to Fit-1 nucleic acid molecules. The Examiner also notes the Applicant's amendment to the claim which removed the terms "selectively" and "stringent conditions". These arguments have been fully considered and are not deemed persuasive. The breadth of the claims is excessive because the claims read on any isolated nucleic acid molecule, of any size, that is capable of hybridizing to the nucleic acid molecule of (i). As written, the claim could read on full-length Fit-1 nucleic acid molecules, or it could read on a fragment of 2-3 nucleotides that share homology to a region of Fit-1. The claims therefore encompass an unreasonably large number of molecules, which includes the Fit-1 nucleic acid molecules disclosed in the specification and those known in the art at the time the invention was made, but also an unreasonably large number of potential fragments with no diagnostic utility. The specification only teaches that hybridization of full-length Fit-1 correlates with cardiovascular disease, and does not teach how to diagnose a cardiovascular disease by hybridization of any other nucleic acid molecule that is capable of hybridizing to Fit-1. A person of ordinary skill in the art would not be able to predict how to diagnose a cardiovascular disease by hybridization of any nucleic acid molecule other than full-length Fit-1, to the nucleic acid molecule of (i). As such, it would require undue experimentation on the part of the skilled artisan to correlate cardiovascular disease with hybridization of the many possible nucleic acid molecules capable of hybridizing to Fit-1.

Claim Rejections - 35 USC § 112, first paragraph – written description

Rejections withdrawn:

1. Rejection of claims 1, 6-8, and 10 under 35 USC § 112, first paragraph, regarding lack of written description for methods of diagnosis of cardiovascular conditions by determining expression of Fit-1 nucleic acids and polypeptides, as set forth on page 6-7 of the prior Office Action mailed on 10/07/2005, is withdrawn in response to Applicant's arguments that several Fit-1 nucleic acid and polypeptide sequences were known in the art at the time the invention was made. Rejection of claim 2 is rendered moot by Applicant's cancellation of the claim.

2. Rejection of claim 10 under 35 USC § 112, first paragraph, regarding lack of written description for methods of diagnosis of cardiovascular conditions by determining expression of peptides that bind the antibody of (iv – claim 8), and an antibody that selectively binds the peptide of (iii – claim 8), as set forth on page 7-8 of the prior Office Action mailed on 10/07/2005, is withdrawn in response to Applicant's arguments that antibodies to Fit-1 peptides were known in the art at the time the invention was made, and that the knowledge in the art, at the time the invention was made, provides structural and sequence features of Fit-1.

Rejections maintained:

3. Claim 10 remains rejected, and new claims 39 and 44-45 are also rejected under 35 USC § 112, first paragraph, regarding lack of written description for methods of diagnosis of cardiovascular conditions by determining expression of Fit-1 nucleic acids and polypeptides, as set forth on page 8 of the prior Office Action mailed on 10/07/2005. The Applicants argue, on p. 18 of the response received on 12/27/2005, that a person of ordinary skill in the art would know of several Fit-1 nucleic acid sequences, and could readily envision nucleic acid sequences capable of hybridizing to Fit-1. These arguments have been fully considered and are not deemed persuasive. As stated above in the rejection of claims 10, 39, and 44-45 for lack of enablement, the claims read on any possible nucleic acid molecule, regardless of size, that is capable of hybridizing to Fit-1. These could include full-length Fit-1 nucleic acids and nucleic acids sharing significant homology to Fit-1, and also 2-3 nucleotide fragments from molecules unrelated to Fit-1. Therefore, Applicants have not fully defined the genus of nucleic acid molecules that are both capable of hybridizing to Fit-1 and whose hybridization to Fit-1 is diagnostic of cardiovascular disease.

Claim Rejections - 35 USC § 112, second paragraph

Rejections withdrawn:

1. Rejection of claim 8 under 35 USC § 112,second paragraph, as being indefinite in regards to "a polypeptide encoded by the nucleic acid", as set forth on page 9 of the prior Office Action mailed on 10/07/2005, is withdrawn in response to Applicants amending the claim to read "a polypeptide encoded by the nucleic acid of part (i).

2. Rejection of claim 10 under 35 USC § 112,second paragraph, as being indefinite in regards to "stringent conditions" as set forth on page 9 of the prior Office Action mailed on 10/07/2005, is withdrawn in response to Applicant's amendments to the claim which have removed the terms "selectively" and ""under stringent conditions".

Rejections maintained:

1. Claims 1, 6-8, and 10 remain rejected, and new, dependent claims 37-48 are also rejected under 35 USC § 112, second paragraph, for being incomplete for omitting essential method steps, as set forth on pages 8 (inadvertently included under 112, first paragraph written description rejections) of the prior Office Action mailed on 10/07/2005. Rejection of claim 2 is rendered moot by Applicant's cancellation of the claim. On page 19 of the response received on 12/27/2005, the Applicants argue that the claimed method does not require measuring a control, because Fit-1 may not be expressed in the blood or serum of healthy patients, or alternatively, that the level of Fit-1 expressed above a certain baseline is considered "increased". These arguments have been fully considered and are not deemed persuasive. The establishment of a "baseline" represents a control to which other data is compared. The claims do not specify any baseline or time period in which the Fit-1 determination will be made. Without knowing what constitutes baseline levels of Fit-1 expression, or without multiple determinations over a period of time, a person of ordinary skill in the art would not be able to determine if Fit-1 expression is increased. The Examiner suggests amending the claims, *without adding new matter*, to add a step which states, for example, "in which Fit-1 levels are measured at various time points to determine aberrant expression."

Claim Rejections - 35 USC § 103

Rejection of claim 10 under 35 USC § 103, as being obvious over the combination of Kumar *et al* and Baumgarten *et al*, as set forth on pages 9-10 of the prior Office Action mailed on 10/07/2005, is withdrawn in response to Applicant's arguments. Although proinflammatory cytokines, such as TNF-α and IL-1, are known to be associated with cardiovascular disease (see Kumar *et al*), and even though TNF-α and IL-1 have been shown to induce Fit-1 expression (see Baumgarten *et al*), the Examiner agrees with the Applicant's assertion that there would be no motivation to directly link Fit-1 expression to cardiovascular disease. In view of the fact that TNF-α induces the expression of over 1000 genes, as argued by the Applicants, the Examiner agrees that there would be no motivation to specifically use Fit-1 expression as a diagnostic marker for cardiovascular disease.

Double Patenting

Claims 1, 6-8, and 10 remain rejected under the judicially-created doctrine of obviousness-type double patenting over claims 1-3, 7, and 9 of copending application 10/435,482. The Examiner acknowledges the Applicant's traversal of the rejection. However, because the claims of the copending application are still pending and have not been withdrawn or cancelled, the rejection is maintained. In addition, new claims 37-48 are rejected over claims 1-3 and 7-11 of copending application 10/435,482.

Conclusion

No claim is allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruce D. Hissong, Ph.D., whose telephone number is (571) 272-3324. The examiner can normally be reached M-F from 8:30am - 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback, Ph.D., can be reached at (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

BDH
Art Unit 1646

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PRIMARY EXAMINER